

SHORT ORIGINAL ARTICLE / *Gastrointestinal imaging*

# Advantages of gadobenate dimeglumine-enhanced MR cholangiography in the diagnosis of post-liver transplant bile leakage

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## KEYWORDS

Gadobenate  
dimeglumine;  
MR cholangiography;  
Liver transplant;  
Bile leakage

## Abstract

**Objective:** To assess the value of magnetic resonance cholangiography with gadobenate dimeglumine (Gd-BOPTA) where there is a suspicion of bile leakage in the post-liver transplant patient.

**Patients and methods:** Eight patients who had undergone a liver transplant underwent 14 MR cholangiograms, five of whom presented bile leakage while the other three had no biliary system complications. The results were compared to conventional bile duct opacification (by endoscopy or t-tube cholangiogram). The analysis covered whether there was opacification of the common bile duct and intrahepatic bile ducts on T1-weighted sequences after an injection of Gd-BOPTA on delayed biliary excretion phase sequences that were carried out on average 74 min after the injection. Enhancing perihepatic collections were also taken into account.

**Results:** Opacification of the bile ducts on delayed-phase MR cholangiogram sequences was always seen in the absence of bile leakage, and was never found when leakage was present. Enhancing perihepatic collections pointed to bile leakage every time.

**Conclusion:** Gd-BOPTA-enhanced MR cholangiography is a simple and non-invasive technique for detecting bile leakage in the post-liver transplant patient.

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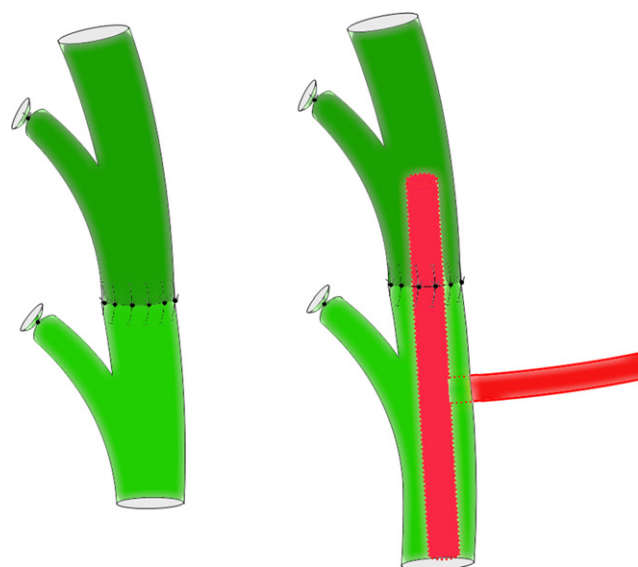
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Complications of the biliary system are foremost in the immediate and later recovery period from a liver transplant, seen in 10–30% of cases [1,2]. The most common complication is bile duct stricture (16%), followed by bile leakage (11%) [3]. The clinical symptoms (bile externalised via a drain or through the scar, abdominal pain, jaundice, fever) and abnormal laboratory findings (cytolysis and cholestasis) are signs that are sensitive, though not very specific, for confirming the presence of an anastomotic bile leakage (Fig. 1).

There are two ways in which to make a diagnosis. On the one hand, there are the non-invasive but minimally specific investigations including sonography, computed tomography (CT), MRI with or without gadolinium chelates, and opacification by t-tube cholangiogram, and on the other, there are invasive investigations such as endoscopic retrograde or percutaneous transhepatic cholangiography, which remain the gold standard techniques. The first group of techniques lack specificity as they usually show subhepatic or perianastomotic "collections" while the second group, and endoscopic retrograde cholangiography in particular, carry a risk of haemorrhage (1.13%), pancreatitis (1.8%), and infection, and they are still not of perfect sensitivity [4,5].

Since mangafodipir trisodium (Teslascan® GE Healthcare, Princeton, NJ) was withdrawn from the market in 2006 [6], the use of hepatocyte-specific gadolinium chelates that are in part excreted through the biliary tract in this indication has been minimally reported in the literature.

The purpose of this article is to report our experience of using gadobenate dimeglumine (Gd-BOPTA) (MultiHance®; Bracco Diagnostics Inc., Princeton, NJ), the only hepatocyte-specific gadolinium chelate that is currently available in France, in order to detect bile leakage in liver transplant patients using a non-invasive method.



**Figure 1.** Duct-to-duct biliary anastomosis preserving the cystic duct stumps with or without Kehr's t-tube (in red).

## Patients and methods

### Patients

Between June 2010 and March 2012, 32 liver transplants were carried out at our centre. Fourteen gadobenate dimeglumine-enhanced (Gd-BOPTA, MultiHance®) MR cholangiograms were carried out in eight patients who had undergone liver transplant for the following reasons: three cases of alcoholic cirrhosis, two cases of decompensated hepatitis C cirrhosis, one of hepatocellular carcinoma in alcoholic cirrhosis, one of fulminant hepatitis, and one of fibrolamellar carcinoma. The patients were four males and four females with a mean age of 47 (27–63 years) (Table 1).

All of the patients showed clinical signs/laboratory study results suggestive of a bile leakage. Six patients out of eight had had a CT scan and all had had a sonogram initially, showing perihepatic collections and an absence of bile duct dilation.

The MR cholangiogram was carried out on average 26 days (17–41 days) after the transplant.

Of these eight patients, five presented a bile leak: four hilar leaks (anastomotic or cystic) confirmed by endoscopic retrograde cholangiography, and one leak along the cut edge of a partial transplant (donor right lobe in a small stature recipient) confirmed by t-tube cholangiography followed by computed tomography.

Therapeutic management consisted of fitting one or several endostents via retrograde endoscopy for the patients who presented an anastomotic bile leakage at the hilum and monitoring for the patient who presented a leak at the cut edge of the lobectomy. During the recovery period, all of the patients gradually improved in terms of clinical signs and laboratory findings, with resolution of the bile leak confirmed using the same imaging modality that led to diagnosis, on average nine weeks (extreme values of 5 and 12 weeks) after the endoscopy treatment. The endostents were removed after the repeat examination.

### Methods

All of the MR cholangiograms were carried out using a 1.5 Tesla system (Optima MR450W, GE medical systems, Milwaukee, Wis) with a phased-array coil. The patients were placed in the dorsal decubitus position with respiratory monitoring and no premedication except for consumption of pineapple juice before the examination in order to block out the signal from gastric juices. The protocol consisted of axial and coronal single shot fast spin echo (SSFSE) T2-weighted sequences during breath-hold (TE = 102 ms, TR 650 ms, slices 4 mm thick, matrix 512 × 512), a 3D MR cholangiography sequence and thick sequential slices in 2D MR cholangiography in the coronal oblique plane (TE = 581 ms, TR = 6000 ms, slices 20 mm thick), and T1-weighted LAVA Flex sequences (Liver Acquisition with Volume Acceleration) with fat saturation, both with and without contrast injection (TE = 3.1 ms, TR = 6.05 ms, slices 4 mm thick, matrix 512 × 512). This sequence was carried out at T = 0, T = 30 s, T = 80 s, T = 4 min, T = 12 min. Finally, a delayed-phase acquisition known as the biliary sequence was carried out at T = 74 min on average [45–120 min] after the injection of Gd-BOPTA (MultiHance®), which allowed the biliary excretion

**Table 1** Detail of patients in the study and their evolution.

Patients	Indication for transplant	Initial MR cholangiogram	Cholangiogram	Treatment
1	Fibrolamellar carcinoma Whole liver	D + 22 Opacification of IHBD and CBD No enhancing perihepatic collections	D + 23 ERC No bile leakage	
2	Alcoholic cirrhosis (alcohol stopped) Whole liver	D + 41 Opacification of IHBD and CBD No enhancing perihepatic collections	D + 46 ERC No bile leakage	
3 Fig. 1	Alcoholic cirrhosis (alcohol stopped) Whole liver	D + 20 Opacification of IHBD and CBD No enhancing perihepatic collections	D + 21 ERC No bile leakage	
4 Figs. 2 and 3	Fulminant hepatitis Partial transplant (left hepatectomy)	D + 18 No opacification of BD Hilar and perihepatic enhancement	D + 16 Opacification study by t-tube cholangiogram, then CT Bile leakage along the hepatectomy line	Monitoring Repeat MR cholangiogram at 3 then 6 weeks, then t-tube cholangiogram with opacification showing no further bile leak at 6 weeks
5 Fig. 4	Alcoholic cirrhosis (alcohol stopped) Whole liver	D + 38 No opacification of BD Hilar and perihepatic enhancement	D + 40 ERC Bile leakage from the native cystic duct stump	Metal endostent placed in situ, removed 10 weeks later Repeat MR cholangiogram showing good opacification of the CBD
6 Fig. 5	Chronic HCV cirrhosis Whole liver	D + 35 No opacification of BD Hilar and perihepatic enhancement	D + 36 ERC Anastomotic bile leakage	Metal endostent placed in situ, MR cholangiogram carried out 5 weeks later no longer found signs suggestive of a leak, meaning the endostent could be removed
7	HCC complicating alcoholic cirrhosis Whole liver	D + 19 No opacification of BD Hilar and perihepatic enhancement	D + 23 ERC Hilar bile leakage	Plastic endostent placed in situ, then replaced by a metal one, removed 12 weeks later MR cholangiogram carried out after this no longer found a leak
8	Alcoholic and HCV cirrhosis Whole liver	D + 17 No opacification of BD Hilar and perihepatic enhancement	D + 18 ERC Anastomotic bile leakage	Metal endostent placed in situ, removed 11 weeks later Repeat MR cholangiogram showing good opacification of the CBD

ERC: endoscopic retrograde cholangiography; IHBD: intrahepatic bile ducts; CBD: common bile duct; BD: bile ducts; HCC: hepatocellular carcinoma.

properties of this gadolinium chelate to be exploited. In between the two sequences at 4 and 12 min, a T2-weighted FSE Fat Sat sequence was taken (TE = 92 ms, TR 9230 ms, slices 5 mm thick).

The dose of gadobenate dimeglumine (Gd-BOPTA) (MultiHance®) injected was 0.05 mmol/kg of body weight, or 0.1 mL/kg at a rate of 2 mL/s, mean dose of 12 cc [6–16 cc].

The MR cholangiograms were interpreted by two gastroenterological and hepatobiliary radiologists working together. There were three signs that they looked for in each case: opacification of the common bile duct on the delayed-phase biliary acquisition; opacification of the intrahepatic biliary tree on the delayed-phase acquisition; delayed-phase enhancement of hilar or perihepatic collections, demonstrated using measurements of signal intensity in the ROI.

## Results

All the examinations were considered possible to interpret in spite of the presence of a few metal artifacts (staples in six cases, and coils in one patient who underwent examination twice) and respiratory artifacts.

The three patients who did not present bile leakage all showed opacification of the common bile duct and the proximal biliary tree as far as the second order intrahepatic bile ducts. No enhancing perihepatic collections were demonstrated in these patients (Fig. 2).

Of the five patients who did present bile leakages, none presented delayed-phase visualisation of the biliary tree or opacification of the common bile duct, irrespective of whether the origin of the leak was anastomotic, cystic, or at the cut edge of the hepatectomy (Figs. 3 and 4). Four of these five patients showed significantly enhancing hilar and perihepatic collections (Fig. 5).

Once the leak was treated or stemmed, repeat MRI scans were carried out on average 9 weeks later (5–12 weeks), and these showed that the common bile duct had become opaque and there was an absence of residual enhancing hilar and perihepatic fluid collections.

## Discussion

Postoperative bile leakages pose a real problem of diagnosis in liver transplant patients. They are a common complication (11% in the literature [3] and 15% in our study) in weakened patients, with a clinical presentation and laboratory study results that are sensitive but non-specific.

The value of gadolinium-based contrast agents with hepatobiliary specificity has been broadly proven in terms of identifying and characterising hepatic lesions, as well as for the morphological exploration of the bile ducts [7,8].

In the context of MR cholangiography, they are useful for their properties of hepatobiliary excretion, which enable an acquisition combining the morphological features of MRI with the functional information of bile duct studies.

The standard MR cholangiogram demonstrates indirect signs relating to the presence of effusion or perihepatic collections and these require careful interpretation in the post-transplant context, as they could be residual ascites, postoperative collections, or localised collections of bile

(biloma). In contrast, hepatobiliary excretion demonstrates a direct sign (opacification of the bile ducts or collections) (Fig. 6).

In our study, the patients that did not present bile leakages, or who had been previously treated with a biliary stent, presented opacification of the common bile duct and the proximal biliary tree. By contrast, none of the patients who did have a bile leakage, irrespective of its origin, presented bile duct opacification and almost none of them (4/5) presented enhancing hilar or perihepatic collections. The gadolinium chelate excreted seemed to leak into the collections rather than stagnating in the bile ducts.

The use of gadobenate dimeglumine (MultiHance®) does not compromise liver function [9–11]. This means that it is possible to use this product in patients in the perioperative period of a liver transplant while still respecting the usual limitations regarding renal function and the risk of nephrogenic systemic fibrosis in patients with severe acute or chronic renal failure (creatinine clearance < 30 mL/min/1.73 m<sup>2</sup>), given that there is a higher incidence of acute renal failure in this group.

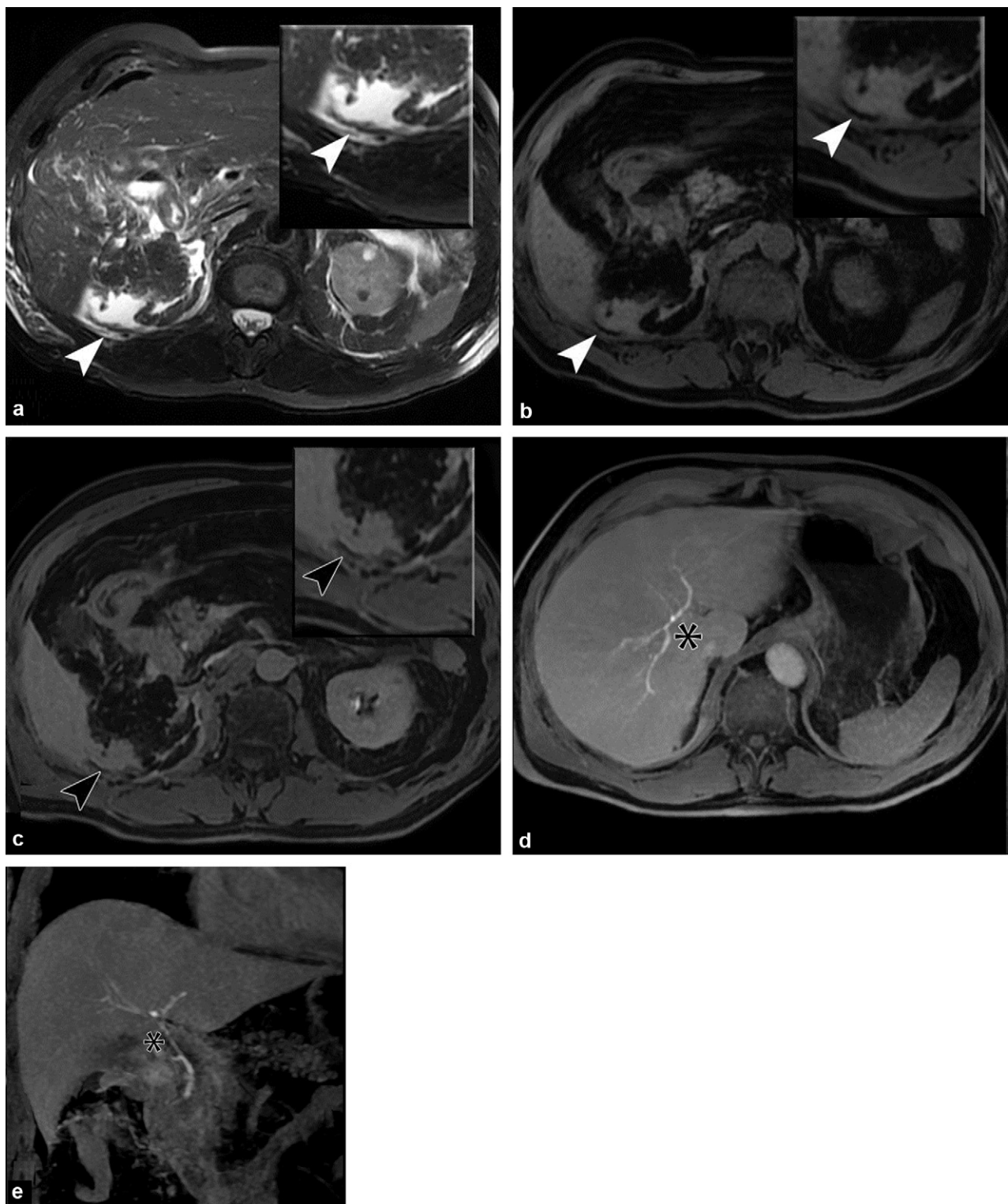
Gadobenate dimeglumine is a gadolinium-based contrast product that is hepatobiliary tract-specific and it has two important properties: firstly, it can diffuse into the extracellular space, while secondly it is actively transported into hepatocytes and subsequently excreted in the bile at a rate of up to 3–5% of the total dose [12].

A dose of 0.05 mmol/kg of body weight or 0.1 mL/kg is recommended for the detection or monitoring of primary hepatic lesions or hepatic tumours [13,14], which equates to half of the dose recommended for exploring the central nervous system and in MRA. This half-dose is made possible by the increased relaxivity of gadobenate dimeglumine in comparison to other extracellular gadolinium-based agents, probably due to its weak capacity to bind with albumin [15]. In our experience, for patients with satisfactory renal function and in view of the low biliary excretion rate, it is preferable to use a dose of 0.1 mmol/kg or 0.2 mL/kg to obtain satisfactory biliary excretion that is visible either in the form of opacification of the common bile duct and visualisation of the biliary tree, or in the form of significantly enhancing perihepatic collections of bile.

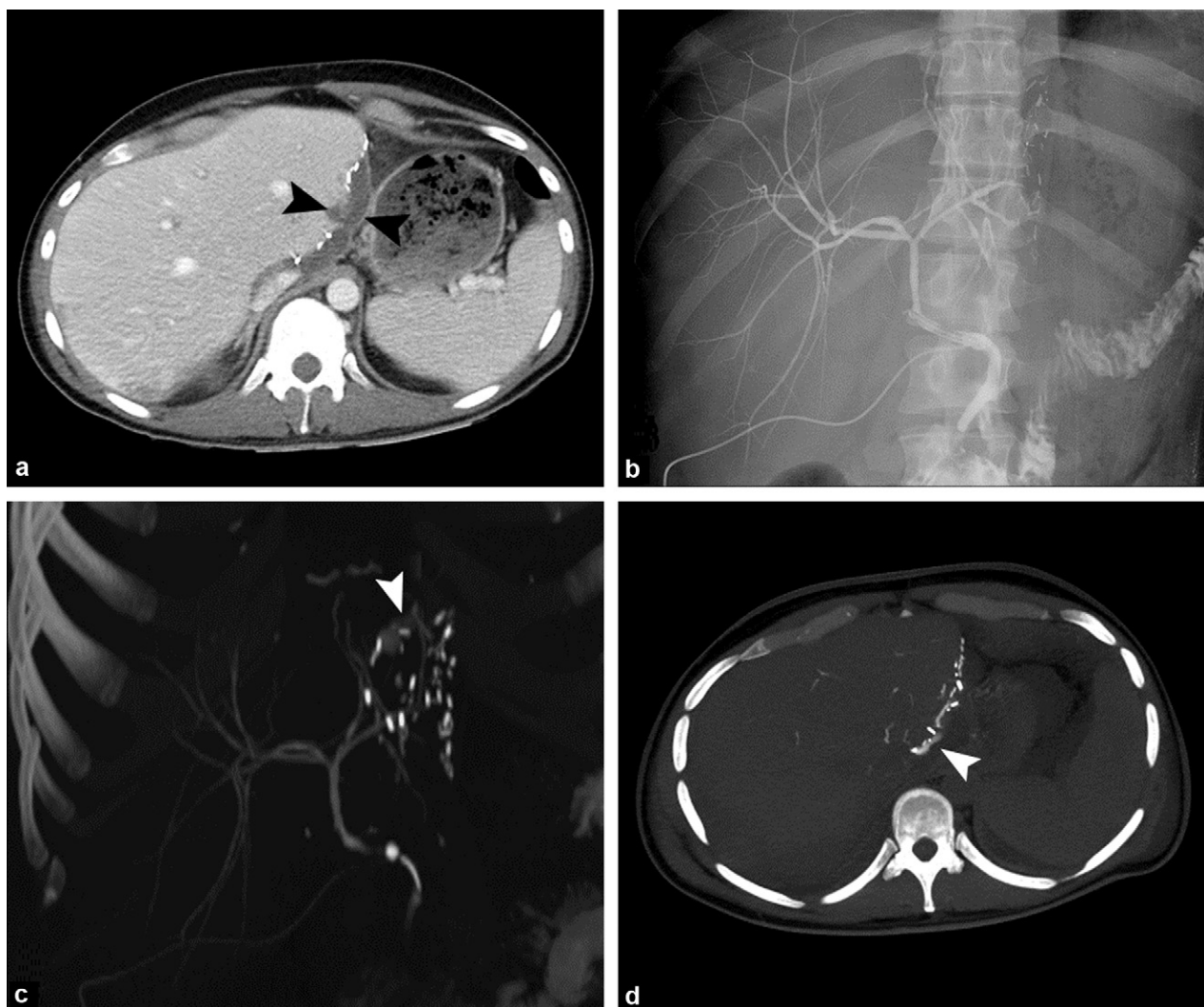
It is possible to take T1-weighted acquisitions during the biliary excretion phase between 45 and 120 min after the injection while achieving sufficient enhancement. In our experience, acquisitions taken at between 55 and 65 minutes provide the best diagnostic information.

Since the withdrawal from the market in 2006 of Mangafodipir trisodium (Teslascan® GE Healthcare, Princeton, NJ) which had a biliary excretion rate of 59%, the only gadolinium-based agent that is in part excreted via the biliary tract that is available in France is gadobenate dimeglumine (MultiHance®). There is one final agent that is not available in France: gadoxetic acid (Primovist® Bayer Healthcare), which has a 50% biliary excretion rate [16]. In contrast to Mangafodipir trisodium (Teslascan®), for which there is plenty of literature concerning this indication, the use of gadobenate dimeglumine (MultiHance®) has not to our knowledge been described. The main limitation on the usage of gadobenate dimeglumine is that its hepatobiliary excretion is delayed in comparison with other products: 1–2 hours for gadobenate dimeglumine





**Figure 2.** A 49-year-old male patient, D + 20 after liver transplant. His clinical picture features cholestasis, cytotoxicity, a fall in haemoglobin levels, and abdominal pain. Sonography and computed tomography found subhepatic collections without active bleeding: a: axial T2-weighted FatSat view demonstrating a collection with high T2 signal intensity (white arrowheads); b: axial T1-weighted LavaFlex view with fat saturation, showing this same collection with T1 isosignal intensity (white arrowheads); c: axial T1-weighted LavaFlex view with fat saturation 57 min after injection of 10 ml of gadobenate dimeglumine does not demonstrate enhancement of this subhepatic blood-containing collection (black arrowheads); d, e: axial and coronal T1-weighted LavaFlex MIP reconstructions in the delayed phase visualising the common bile duct and proximal biliary tree (asterisk). The endoscopic retrograde cholangiography carried out afterwards confirmed the absence of bile leakage.

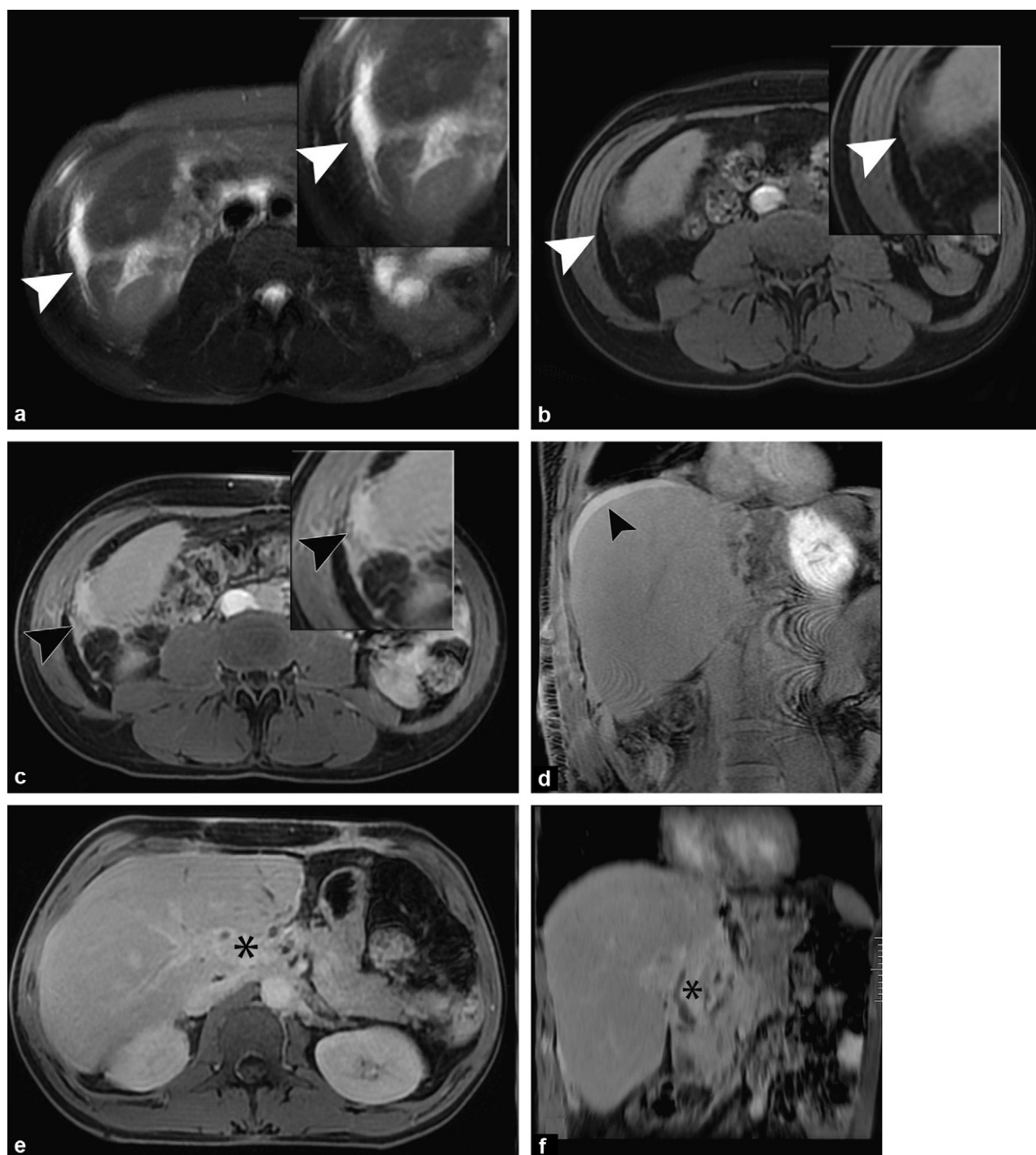


**Figure 3.** A 29-year-old male patient, recipient of a partial liver transplant (left hepatectomy), who presented gradual worsening of cutaneous and scleral jaundice and hyperbilirubinaemia up to D + 16: a: axial portal phase iodine contrast-enhanced CT image demonstrating a collection next to the cut edge of the left hepatectomy (black arrowheads); b: t-tube cholangiogram, no bile leakage is evident from the left bile ducts that are reported to be slightly irregular; c, d: computed tomography exploration carried out following the t-tube cholangiogram, coronal and axial MIP reconstruction that clearly visualises the bile leakage at the cut edge of the lobectomy (white arrowheads) next to the surgical clips.

(MultiHance®) as against 15 min for the previously used mangafodipir trisodium (Teslascan®), although this did not allow for dynamic studies of liver tumours or primary hepatic lesions, and 10 min for gadoxetic acid (Primovist®) [8].

Given the excellent correlation between bile leakage of any origin and the simple signs brought together in our study, testing in a larger sample of patients would appear to be

required in order to confirm the sensitivity and specificity of this set of signs (bile duct opacification: no bile leakage. No bile duct opacification: bile leakage). Nonetheless, gadobenate dimeglumine's (MultiHance®) low rate of excretion of 3–5% of the total dose does not, in our experience, lead to a precise visualisation of the path of the fistula or the origin of the leak, as Mangafodipir trisodium (Teslascan®) did [6].



**Figure 4.** Same patient as in Fig. 2. Forty-eight hours after the cholangiogram, an MRI was carried out with 16 ml of gadobenate dimeglumine and delayed-phase acquisitions taken 120 minutes after the injection: a, b: axial T2-weighted FatSat and axial T1-weighted LavaFlex fat saturation images, showing in particular a subhepatic collection with high T2 and low T1 signal intensity (white arrowheads); c–f: axial and coronal T1-weighted LavaFlex fat saturation images, delayed-phase acquisitions (120 min) after the gadobenate dimeglumine injection, enhancing subhepatic and perihepatic collections (black arrowheads) and no bile duct opacification (asterisk).





**Figure 5.** 63-year-old female patient, with a hilar collection persisting at D + 38. MRI carried out with 9 ml of gadobenate dimeglumine and delayed-phase acquisitions taken 62 minutes after the injection: a, b: axial T2-weighted FatSat and T1-weighted LavaFlex fat saturation images demonstrating a hilar collection with high T2 and low T1 signal intensity (white arrowhead); c, d: axial reconstruction and coronal T1-weighted LavaFlex fat saturation image, showing enhancing hilar collections (black arrowheads) and no opacification of the common bile duct (asterisk); e: endoscopic retrograde cholangiogram confirming the presence of a bile leakage (black arrows) from the native cystic duct stump. Following the cholangiogram, the patient was fitted with a covered metal biliary stent; f: 10 weeks after the covered metal biliary stent was fitted, the patient's improvement in terms of clinical signs and laboratory results permitted its removal. Cholangiography no longer found a bile leakage. The MRI that was carried out subsequently with delayed-phase acquisition at 74 minutes after injection of 9 ml of gadobenate dimeglumine demonstrated that the hilar collections had regressed as well as showing opacification of the common bile duct, providing further confirmation that the leak had resolved.





**Figure 6.** A 54-year-old female patient in whom monitoring using sonography and computed tomography demonstrated hilar collections, which were associated with cholestasis and hepatic cytolysis. An MR cholangiogram was carried out at D + 35: a: MIP reconstruction of a 3D biliary MRI that clearly visualises the native ectatic bile duct and the narrow transplanted bile ducts. Perianastomotic collections are present (white arrowhead) that probably correspond to a biloma (indirect sign of bile leakage); b: coronal T1-weighted LAVA-Flex image with fat saturation, delayed-phase acquisition taken 110 min after gadobenate dimeglumine injection showing enhancing hilar collections with peri-biliary contrast uptake (black arrowheads) and no bile duct opacification (asterisk) (direct signs suggestive of a leakage); c: endoscopic retrograde cholangiography carried out at D + 36 confirmed the leak and enabled an endostent to be placed in situ.

## Conclusion

Carrying out a delayed-phase biliary sequence 60 min after administration of gadobenate dimeglumine (Gd-BOPTA) (MultiHance®), the only product currently available in France that is in part excreted by the biliary tract, allows bile leakage to be demonstrated in post-liver transplant patients. Using this non-invasive technique for diagnostic purposes would allow endoscopic retrograde cholangiography to be reserved for patients who need therapeutic management, i.e. those who require one or more biliary endostents to be inserted once the leakage is confirmed.

## Disclosure of interest

The authors have not supplied their declaration of conflict of interest.

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